Remarks/Arguments

No new matter is believed to be added by this Amendment Support for changes to the claims and specification may be found throughout the application as filed, for instance as set forth below. No new claims are believed to be independent and distinct from claims previously claimed and examined in this application.

In the Claims

Claim 37 element (d) is amended to remove the term "a chemical irritant" and to provide correct antecedent basis thereafter. Claim 58 is amended in view of this amendment to claim 37.

Claim 64 is corrected to read "mg/cm^2", in response to the objection raised at page 2 of the present Action.

New claims 80-84 are presented. New claim 80 limits the present invention to a transdermal carrier having a compound which specifically has or induces cytokine or anti-cytokine activity and an antigen/allergen associated with a penetrant. This claim is similar to claim 39, previously canceled in this application. In the Office Actions issued in this application on May 25, 2006 and July 18, 2007, the Examiner rejected claim 39 under 35 U.S.C. § 112 as vague and indefinite, and requested clarification of the meaning of the association of a penetrant with for instance an antigen according to the present invention.

To facilitate prosecution of the application, Applicant respectfully notes that new claim 80 complies with 35 U.S.C. § 112, and is not vague and indefinite. Applicant sets forth examples of the term "associated with" or variations thereof from the application as filed, to clarify the meaning of the term in the context of the present invention:

- Page 7 lines 8-11 of the application as filed states that carriers (penetrants) and "material associated with them" pass through the skin without significant perturbation of the skin.
- Page 13 lines 19-21 mentions an antigen may be "free" (not associated) or "associated with a carrier". Also, page 13 line 19 refers to a hapten "coupled" to a carrier, indicating that "coupling" falls within the meaning of being "associated with" a carrier.
- The paragraph bridging pages 14 and 15 of the application as filed discusses "loading" a penetrant with an antigen or other substances; once loaded, the (ex.) antigen would be associated with the penetrant. See also page 27 lines 18-22, describing "loading" a suspension of antigen-free penetrants with antigen, so the penetrants and antigen are associate with each other prior to administration.
- The paragraph bridging pages 17-18 states that when macromolecular antigens and (ex.) cytokines are associated with penetrants, they can cross the skin and elicit a therapeutic or prophylactic response.

- Page 21 lines 22-27 discusses the flux of penetrants associated with an immunogen (immuno-penetrant) through various pores in a well-defined barrier. The immunogen and the penetrant are associated (not free of each other), so that they go through the pore together. See also page 21 lines 31-34, discussing immunogen-free penetrant suspensions.
- Page 22 lines 27-29 of the application as filed discloses that the association of antigen and (ex.) cytokine with a penetrant is a preferred embodiment of the present invention.

In the July 18, 2007 Action (pages 11-12), the Examiner expresses concern that it is not clear how claim 39 was different from claim 37. In the event that the Examiner believes that concern applies to new claim 80, Applicant wishes to note that claim 37 does not expressly require the association of (ex.) antigen with a penetrant. In claim 37, the antigen may be free of the penetrant, although in the same composition. In new claim 80, the antigen is not free of the penetrant, but rather is associated with it. The co-existence of claim 37 and the new claim means that, for instance, penetrants and antigens in a composition of the present invention may be free of each other while in the same composition (claim 37), or associated with each other (new claim 80).

As mentioned above, new claim 80 is similar to previously pending claim 39. In keeping with statements regarding the Office Action filed March 14, 2006, Applicant notes that new claim 80, although not specifically reciting Species A, B or C, is readable on each elected species. New claims 81, 82, 83 and 84 also do not specifically recite Species A, B or C, but are readable on each species.

Several claims, currently withdrawn, are amended to place the claims in condition for rejoinder. With this Amendment, all withdrawn claims are believed to be in condition for rejoinder.

In the Specification

Reference to US and/or PCT Publication Numbers are added at pages 1, 14 and 20.

An incorrect reference to Figure 10 is deleted from Examples 24-25 (Page 43 lines 16-17). As may be seen from the application as filed, Examples 24-25 refer in part to penetrants including IFN-gamma, GM-CSF and IL-4, and Figure 10 refers in part to penetrants having TT/CT. Figure 10 is correctly referred to at page 47 line 1 of the application as filed, Examples 73-82.

Response to rejection under 35 U.S.C. § 102(b)

In the present Action, claims 37, 38, 40-41, 58-59 and 65 are rejected under 35 U.S.C. § 102(b) as anticipated by Paul *et al.* (Vaccine Research 4:145-164 (1995); hereafter "Paul"), for reasons set forth in the Office Action mailed in this application on May 1, 2008. The previous Action states in part that Paul discloses a transdermal carrier known as a transfersome having the same composition as the claimed carrier, an antigen (BSA) and a compound which induces cytokine activity (lipid A). The present Action further states that Paul's transfersomes include sodium cholate and triethanolamine, both of which are irritants. For these reasons the Examiner concludes that Paul discloses the present invention.

To facilitate prosecution of this application, Applicant deletes the term "a chemical irritant" from pending claim 37, and further amends the claim to read "a fragment or a derivative of a chemical irritant", in keeping with US practice regarding antecedent basis . Applicant respectfully submits that claim 37 is novel over Paul therefore and, similarly, that claims 38, 40-41, 58-59 and 65 are novel over Paul. Applicant notes this amendment is not meant to indicate acquiescence to the above-mentioned rejection.

Response to rejection under 35 U.S.C. § 103(a)

In the present Action, the Examiner rejects claims 37-38, 40-45, 47-48, 50, 55, 58-60 and 62-66 as obvious under 35 U.S.C. § 103(a) over Glenn *et al.* (WO 98/20734; hereafter "Glenn") in view of Paul. With regard to independent claim 37, the Examiner states that Glenn discloses a transdermal vaccine that contains tetanus toxoid and interleukin-12, citing Glenn's abstract as well as Glenn page 16 lines 15-17, the paragraph bridging pages 15-16, and page 18 lines 15-30; and that Glenn differs from the present invention in that the transdermal vaccine does not comprise a carrier of the present invention. The Examiner further states that Paul discloses a transdermal carrier of the present invention, and that it would be obvious to one of skill in the art to use Paul's carrier in Glenn's vaccine to take advantage of the high drug transfer efficacy of the transfersomes. Also, page 10 lines 5-8 of the Action state that the Examiner is not suggesting the inventions of Glenn and Paul could be literally combined, but that the antigen and adjuvant of Glenn could be used in the transfersomes of Paul, with the conclusion that there is no incompatibility between the references that would prevent such a combination.

Applicant notes that Glenn teaches administering a simple aqueous solution with an antigen and an adjuvant to transdermally deliver an antigen via passive diffusion/absorption into the stratum corneum, and thus provide a protective immune response to the antigen. See e.g. Glenn page 3 lines 25-37, page 11 lines 5-11, page 12 line 24-page 13 line 1. Glenn further teaches that an antigen can act as its own adjuvant (page 8 lines 7-12), and that bAREs (bacterial ADP-ribosylating exotoxins) are preferred adjuvants for antigen delivery (page 11 lines 5-11).

See in particular Glenn Table 1 (page 43), showing amounts of anti-CT (Cholera toxin) IgG antibodies generated by the application of Cholera Toxin ("CT"; a bARE) in saline to skin with no other antigens/adjuvants present, and Table 12 (page 55), showing that the beta-subunit of CT generates autoantibodies and that the alpha-unit of CT does not. Glenn Table 8 (page 50) shows IgG antibodies generated against CT as well as 2 other bAREs – LT and ETA. Glenn Table 13 (page 56) shows that the bARE diphtheria toxoid (DT) did not generate autoantibodies, but that pertussis toxin (PT; a bARE) acting as adjuvant for DT did allow for the generation of anti-DT antibodies. In view of this and other data, taking Glenn as a whole, one skilled in the art would likely find that the direct application of bAREs having specific subunits to the skin may provide for some transdermal IgG generation.

However, Glenn Example 15 (page 57; no Table) discloses that the application of 50 ug tetanus toxoid (TT), which is not a bARE, with 100 ug CT did not result in the generation of anti-TT IgGs in 80% (4 of 5) mice tested. Of the one mouse where anti-TT IgGs were found, the amount was quite low – 443 ELISA units, which is approximately 1.6% relative for instance to anti-CT IgGs produced by CT alone (Table 1; 27,482 ELISA units). Consider also Glenn Example 23 and Table 19 (pages 69-70), disclosing the application of a solution of 100ug CT, 50ug TT and 83ug DT to the skin of 5 mice. While tens and

hundreds of thousands of anti-CT and anti-DT IgG ELISA units were detected (CT mean: 76,535 and DT mean: 86,528), the mean amount of anti-TT IgGs was 47 (according to Applicant's calculations, about 0.06% and 0.05% of anti-CT and anti-DT IgGs, respectively). Glenn points out at page 69 lines 19-21 that one mouse displayed anti-TT antibody ELISA units of 342, about 80 times the level of IgG detected in unimmunized animals (according to Applicant's calculations, about 0.45% and 0.40% of CT and DT IgGs, respectively). One skilled in the art would also note that the other 4 mice tested had apparently similar and much lower amounts of anti-TT IgG (21, 30, 36, 30 ELISA units; mean = 29 ELISA units) (according to Applicant's calculations, on average, about 0.04% and 0.03% of CT and DT IgGs, respectively). Comparable results were shown with an influenza antigen at Glenn Example 21 and Table 17 (pages 67-68), where Glenn states in part that "influenza alone did not induce an antibody response" where the influenza antigen elicited a geometric mean of 20 IgG ELISA units. Finally, see Glenn Example 28/Table 23 (pages 75-77), wherein TT is shown to be a poor adjuvant when administered with DT, whereas CT was (as in other Examples) an excellent adjuvant.

Despite a few general statements to the contrary, taking Glenn as a whole, Glenn teaches one skilled in the art that TT does not appear to be a good candidate for transdermal delivery to provide a protective immune response, as an antigen or as an adjuvant (or both), at least in view of data showing TT elicits no immune response or very weak immune response when transdermally applied alone or with a bARE such as CT. Glenn particularly teaches away from the combination of TT with IL-12 as adjuvant (a non-bARE), because Glenn generally teaches that a bARE may help elicit IgG production against a non-bARE antigen (and IL-12 is not a bARE), where TT is a very poor antigen even when administered with a bARE.

See also for instance Glenn Example 29 (pages 78-80), disclosing mice having anti-CT IgGs in amounts of 15,000 (challenge #1) and 41,947 (challenge #2) ELISA units had, when exposed to CT, a combined survival rate of 61%. Assuming these amounts of IgGs are indicative of a potentially protective immune response in the practice of Glenn's invention, one skilled in the art would be even more likely to find that Glenn teaches TT is not a good candidate for noninvasive transdermal immunization, regardless of the teachings of Paul *et al*.

In contrast to Glenn, the present invention shows a strong immune response to TT administered as an antigen. As mentioned above, the skilled person would be taught away from using TT in a transdermal vaccine, in view of Glenn's teaching that TT does not stimulate a strong immune response when transdermally applied.

At least in view of the foregoing, Applicant respectfully submits that one skilled in the art would not combine Glenn and Paul in either manner described by the Examiner, but rather would be taught away from transdermal administration/immunization with TT and IL-12.

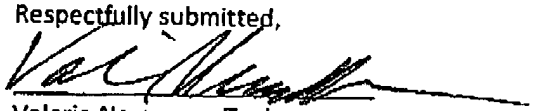
In addition to the foregoing, Applicant notes that new claim 80 is directed to a penetrant having antigen/allergen (c) and compound (b) associated with it (for instance, inside the penetrant droplet, part of the penetrant layer, or otherwise directly adjacent to and/or touching the penetrant). Applicant respectfully notes that as the Examiner was concerned with the meaning of claim 39 (similar to new claim 80) in previous Actions, no explanation as to whether claim 39 was obvious under 35 U.S.C. 103 appears to have been provided by the Examiner. Applicant respectfully submits that one skilled in the art would not find the invention of this claim obvious in view of the cited documents, and requests

allowance of the claim. In the event that the Examiner considers new claim 80 to be obvious under 35 U.S.C. § 103, Applicant respectfully requests that the Examiner provide reasons for such rejection.

Applicant respectfully submits that the present Amendment is fully responsive to the pending Action and places the present application in better condition for allowance. Applicant respectfully requests that the Examiner allow the application to proceed to grant therefore.

In the event that the Examiner maintains any rejection under 35 U.S.C. 103, the Examiner is respectfully requested to restate the rejection, particularly in view of statements made at the top of page 10 of the pending Action (discussed above) and in view of the pending claims. In the event that the Examiner has any questions or concerns regarding this Amendment, the Examiner is invited to contact the below-signed representative by telephone to discuss.

Respectfully submitted,



Valerie Neymeyer-Tynkov
Reg. No. 46,956
Neymeyer-Tynkov LLC
20 N. Clark St. Suite 600
Chicago, IL 60602
Phone: 312/965-1969